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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,871	08/18/2006	Rene Roscher	27579U	3799

34375 7590 02/09/2012

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ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
02/09/2012	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RENE ROSCHER and CHRISTOPH KARL

Appeal 2012-000379
Application 10/589,871
Technology Center 1600

Before DEMETRA J. MILLS, STEPHEN WALSH, and
JACQUELINE WRIGHT BONILLA, *Administrative Patent Judges*.

BONILLA, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims directed to a pharmaceutical formulation consisting of a salt of glycopyrronium, ciclesonide, and lactose monohydrate. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The invention relates to a pharmaceutical dry powder formulation consisting of a pharmaceutical acceptable salt of an enantiomerically enriched R,R-form of glycopyrronium in combination with ciclesonide and lactose monohydrate.

Claims 1, 4, 8-11, and 19 are on appeal. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Independent claim 1 is representative and reads as follows:

> 1. A pharmaceutical formulation consisting of a pharmaceutical acceptable salt of glycopyrronium in combination with ciclesonide, and lactose monohydrate,
>
> wherein the pharmaceutical acceptable salt of glycopyrronium is the enantiomerically enriched R,R-form, (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium,
>
> wherein the enantiomerically enriched R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee), and
>
> wherein the pharmaceutical formulation is a fixed combination as a dry powder.

Claims 1, 4, 8-11, and 19 stand rejected under 35 U.S.C. 103(a) as being obvious over Noe et al. (U.S. Pat. No. 6,613,795 B2) in view of Postma et al.[1]

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[1] Postma et al., *Treatment of Asthma by the Inhaled Corticosteroid Cirlesonide Given Either in the Morning or Evening*, 17 Eur. Respir. J. 1083-1088 (2001)

Issue

The issue is whether one of skill in the art would have been motivated to make the formulation recited in claims 1, 4, 8-11, and 19 by combining a dry powder formulation of a salt of (3R,2'R) glycopyrronium and lactose monohydrate as described in Noe, with an inhalable form of ciclesonide as described in Postma.

Findings of Fact

1. Noe discloses a dry powdered formulation consisting of (3R, 2'R)-3-[cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium salt and lactose monohydrate. *See, e.g.*, Noe, col. 17, ll. 13-32, (Example 11a) and other Examples.

2. Noe describes "enantiomerically pure esters enantiomerically enriched to an enantiomeric purity of 90% minimum enantiomeric excess (ee)" including the (3R,2'R) form. (Noe, col. 3, ll. 11-16).

3. Noe teaches that enantiomerically pure esters (including the 3R,2'R form) of glycopyrronium salts are useful for the treatment of obstructive respiratory diseases such as bronchial asthma. (*Id.* at col. 9, ll. 62-67).

4. Claims 10 and 11 of Noe likewise define a method of treating obstructive respiratory diseases, such as bronchial asthma, using the 3R,2'R form of glycopyrronium salt in the form of a dry powder formulation.

5. As noted by Appellants (Reply Br. 5-6), Noe teaches that the enantiomeric forms of glycopyrronium can be "employed at a particularly low dosage, thus minimizing side effects," and therefore "afford therapeutic results more efficiently, and have a considerably reduced potential for side

effects," as compared to mixtures of stereoisomers or racemates. (Noe, col. 9, ll. 18-23; 57-60).

6. Postma discloses the use of ciclesonide for the treatment of asthma, stating that "[c]iclesonide is currently developed for once-daily dosing in patients with mild-to-moderate asthma." (Postma, 1083, 2nd col.).

7. In the study described in Postma, bronchial asthma patients inhaled 200 µg ciclesonide once a day (either in the morning or evening). (*Id.* at 1084, 1st col.).

8. Postma teaches that in the presented study, "[e]ight out of 209 randomized patients (3.8%) in total (four in each group) experienced lack of efficacy." (*Id.* at 1086, 2nd col.).

9. Postma further teaches that "the investigators and patients rated ciclesonide as being 'very effective' or 'effective' in 61% and 63%, respectively, of the patients treated in the morning, and in 71% and 63% with regard to the evening administration." (*Id.*)

10. Postma also states that "the safety data of the current trial suggest that ciclesonide was well tolerated," which "is in line with the results of a study in healthy volunteers where the 24-h mesor for serum cortisol under ciclesonide (800 µg), given either in the morning or in the evening for one week, was 2-6% lower compared to placebo indicating that ciclesonide lacks relevant systemic effects." (*Id.* at 1087, 2nd col.).

Principles of Law

An obviousness analysis compares the claimed invention and the prior art to determine whether "the subject matter as a whole would have been obvious at the time the invention was made" to a person having ordinary

skill in the art. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed. Cir. 2006). The ultimate question of obviousness is one of law, based upon factual inquiries set forth in the *Graham* case: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of non-obviousness, if any. *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966).

As noted by the U.S. Supreme Court in *KSR*, obviousness requires the showing that a person of ordinary skill at the time of the invention would have selected and combined prior art elements in the normal course of research and development to yield the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). In addition, there must be "an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 418. Such a reason may be found in "interrelated teachings of multiple patents; the effects of [design or marketplace] demands . . . and the background knowledge possessed by a person having ordinary skill in the art." *Id. KSR* notes that obviousness can be determined with reference to "the inferences and creative steps that a person of ordinary skill in the art would employ." (*Id.* at 418.)

As discussed by our reviewing court's predecessor, the U.S. Court of Customs and Patent Appeals, it is prima facie obvious to combine two compositions where each is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Kerkhoven* 626 F.2d 846, 850 (C.C.P.A. 1980) (citing *In re Susi*, 440 F.2d 442, 445 (C.C.P.A. 1971); *In re Crockett*, 279

F.2d 274, 276-77 (C.C.P.A. 1960)); *see also Merck & Co., Inc. v. Biocraft Labs, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) ("Given the prior art teaching that both amiloride and hydrochlorothiazide are natriuretic, it is to be expected that their co-administration would induce more sodium excretion than would either diuretic alone"). In *Crockett*, the court addressed obviousness based on references teaching that each relevant compound had certain relevant activity (i.e., each promoted formation of a nodular structure in cast iron). In that case, the court concluded that:

> it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other. Even assuming … that the two together produce an effect somewhat greater than the sum of their separate effects, we feel that the idea of combining them would flow logically from the teaching of the prior art and therefore that a claim to their joint use is not patentable.

Crockett, 279 F.2d at 276.

Later in *KRS*, the Supreme Court followed up by stating that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. In addition, "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious." *Id.* at 417 (quoting *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 282 (1976)). The Court contrasted these situations with those where "elements worked together in an unexpected and fruitful manner" or created "some new synergy," which would support a finding of non-obviousness. *KSR*, 550 U.S. at 416-17 (citing *United States v. Adams*, 383 U.S. 39, 50-52

(1966); *Anderson's–Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 60-62 (1969)).

Analysis

Claim 1 recites a dry powder pharmaceutical formulation consisting of an enantiomerically enriched R, R-form (3R,2'R) of salt of glycopyrronium in combination with ciclesonide and lactose monohydrate, where the R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee).

Noe teaches a dry powdered formulation consisting of the (3R, 2'R) form of a glycopyrronium salt and lactose monohydrate, and its use for the treatment of asthma. (FF 1, 3-4.) In this context, Noe also describes "enantiomerically pure esters enantiomerically enriched to an enantiomeric purity of 90% minimum enantiomeric excess (ee)" including the (3R,2'R) form. (FF 2.) Thus, as noted by the Examiner (Ans. 7), Noe discloses every element of claim 1, except that it does not describe ciclesonide.

Postma, however, discloses ciclesonide, also for the use of treating asthma. As discussed above, it is prima facie obvious to combine two compositions where each individual composition is taught by the prior art to be useful for the same purpose, and the combination forms a third composition that is to be used for the very same purpose. *In re Kerkhoven* 626 F.2d 846, 850 (C.C.P.A. 1980); *see also KSR*, 550 U.S. at 416-17 (stating that a combination of known elements is obvious when it "'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an

arrangement"). Here, claim 1 is directed to a composition combining the compositions of Noe and Postma, where the combination is to be used for the very same purpose (i.e., to treat asthma) as taught for each of the compositions in the prior art references.

In light of the teachings in Postma and Noe regarding the intended uses of ciclesonide and the formulation of the (3R,2'R) form of glycopyrronium salt and lactose monohydrate, "it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other." *Crockett*, 279 F.2d at 276. Thus, like the court in *Crockett*, "we feel that the idea of combining them would flow logically from the teaching of the prior art." (*Id.*).

In arguing their case, Appellants refer to teachings in Noe indicating that enantiomeric forms of glycopyrronium, when used alone, are useful "at a very low dosage with minimal side effects." (Reply. Br. 6). Thus, according to Appellants, "the ordinary skilled artisan armed with this knowledge would not likely have any motivation to combine this particular compound with any other compound to perhaps achieve better results or a more favorable dosing or side effect profile." (*Id.* at 7).

Likewise, Appellants assert that Postma taught that ciclesonide administered once-daily had a rating of "very effective" or "effective" in 61-71% of asthma patients tested, and that safety data indicated the drug was "well tolerated" with "a low risk for systemic effects." (*Id.* at 7-8). Thus, according to Appellants, "the ordinary skilled artisan armed with this knowledge would not likely have any motivation to combine ciclesonide

with any other compound to perhaps achieve better results or a more favorable dosing or side effect profile." (*Id.* at 8).

Again, both Noe and Postma individually described the respective compounds as useful for the treatment of the same condition, bronchial asthma. Appellants provide no evidence that the two compositions, or the claimed formulation as a whole, "worked together in an unexpected and fruitful manner" or created "some new synergy," which could support a finding of non-obviousness. *See KSR*, 550 U.S. at 416-17. Appellants likewise provide no evidence of a teaching away in the prior art of combining the two compositions described in Noe and Postma, nor any other evidence of secondary considerations in support of non-obviousness.

Rather, Appellants argue that because each composition alone worked so well with little side effects, those skilled in the art would have never had a reason to use the two compositions in combination. Appellants do not suggest, nor provide evidence indicating, however, that either composition alone was 100% effective in 100% of asthma patients. For example, as acknowledged by Appellants (Reply Br. 7), Postma disclosed that ciclesonide failed to work in 3.8% of the patients. (FF 8.) In addition, Postma described a rating of ciclesonide of "very effective" or "effective" in 61% to 71% of the patients. (FF 9.) In other words, despite high ratings, ciclesonide exhibited a rating of less than "effective" in a significant number of patients. Thus, absent evidence to the contrary, we conclude a skilled artisan would have had a reason to believe that at least some patients would benefit from the use of an additional composition, such as the composition taught in Noe, also known to be effective in the treatment of asthma.

We conclude that claim 1 "'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement." *KSR*, 550 U.S. at 417 (quoting *Sakraida*, 425 U.S. at 282). Appellants have combined two prior art compositions (i.e., a dry powder formulation of a salt of (3R,2'R) glycopyrronium and lactose monohydrate as taught in Noe, with an inhalable form of ciclesonide as taught in Postma) for use for the exact purpose taught in the prior art references for each composition, i.e., to treat asthma. Thus, the combination of Noe's dry powdered formulation and Postma's ciclesonide would have been obvious to those skilled in the art.

Conclusion of Law

Because one would have been motivated to combine the dry powder formulation of a salt of (3R,2'R) glycopyrronium and lactose monohydrate as taught in Noe, with the inhalable form of ciclesonide as taught in Postma, particularly for use in the treatment of asthma as described by both references, we agree with the Examiner that claim 1 is obvious over these references. Claims 4, 8-11, and 19 fall with claim 1.

SUMMARY

We affirm the rejection of claims 1, 4, 8-11, and 19 under 35 U.S.C. §103(a) as unpatentable over Noe in view of Postma.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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